Impact of prior and projected climate change on US Lyme disease incidence

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Abstract

Lyme disease is the most common vector-borne disease in temperate zones and a growing public health threat in the United States (US). The life cycles of the tick vectors and spirochete pathogen are highly sensitive to climate, but determining the impact of climate change on Lyme disease burden has been challenging due to the complex ecology of the disease and the presence of multiple, interacting drivers of transmission. Here we incorporated 18 years of annual, county-level Lyme disease case data in a panel data statistical model to investigate prior effects of climate variation on disease incidence while controlling for other putative drivers. We then used these climate-disease relationships to project Lyme disease cases using CMIP5 global climate models and two potential climate scenarios (RCP4.5 and RCP8.5). We find that interannual variation in Lyme disease incidence is associated with climate variation in all US regions encompassing the range of the primary vector species. In all regions, the climate predictors explained less of the variation in Lyme disease incidence than unobserved county-level heterogeneity, but the strongest climate-disease association detected was between warming annual temperatures and increasing incidence in the Northeast. Lyme disease projections indicate that cases in the Northeast will increase significantly by 2050 (23,619 ± 21,607 additional cases), but only under RCP8.5, and with large uncertainty around this projected increase. Significant case changes are not projected for any other region under either climate scenario. The results demonstrate a regionally variable and nuanced relationship between climate change and Lyme disease, indicating possible nonlinear responses of vector ticks and transmission dynamics to projected climate change. Moreover, our results highlight the need for improved preparedness and public health interventions in endemic regions to minimize the impact of further climate change-induced increases in Lyme disease burden.

Keywords: Lyme disease, climate change, *Ixodes scapularis, Ixodes pacificus,* least squares dummy variables, disease projections

Introduction

Arthropod-transmitted pathogens pose a severe and growing threat to global public health (World Health Organization 2014). Because vector life cycles and disease transmission are highly sensitive to abiotic conditions (Mattingly 1969, Sonenshine and Roe 2013), climate change is expected to alter the magnitude and geographic distribution of vector-borne diseases (Kilpatrick and Randolph 2012, World Health Organization 2014). Climatic changes, in particular warming temperatures, have already facilitated expansion of several vector species (e.g., Purse et al. 2005, González et al. 2010, Roiz et al. 2011, Clow et al. 2017a), and have been associated with increased vector-borne disease incidence (e.g., Loevinsohn 1994, Subak 2003, Hii et al. 2009). Identifying areas of high risk for current and future vector-borne disease transmission under climate change is critical for mitigating disease burden. However, the presence of interacting drivers of disease transmission such as land use change and globalization, and the complex ecology of vector-borne diseases make the effort to measure and predict effects of climate on vector-borne disease incidence challenging (Rogers and Randolph 2006, Tabachnick 2010, Mills et al. 2010, Ostfeld and Brunner 2015, Lafferty and Mordecai 2016).

This challenge is particularly apparent in the case of Lyme disease, the most common vector-borne disease in temperate zones (Kurtenbach et al. 2006, Rizzoli et al. 2011, Rosenberg et al. 2018), because transmission depends on a complex sequence of biotic interactions between vector and numerous host species that may respond differently to environmental change (Ostfeld 1997). In the United States (US), Lyme disease is caused by the bacteria *Borrelia burgdorferi*, and is vectored by two tick species: *Ixodes scapularis* in the eastern and midwestern US and *Ixodes pacificus* in the western US. After hatching from eggs, both tick species have three developmental stages—larva, nymph, and adult—during which they take a single blood meal from a wide range of vertebrate hosts before transitioning to the next developmental stage or reproducing (Sonenshine and Roe 2013). This life cycle takes 2-3 years to complete, 95% of which is spent at or below the ground surface in diapause, seeking a host, digesting a blood meal, or molting (i.e., off the host) (Sonenshine and Roe 2013, Ostfeld and Brunner 2015).

Given their long life spans, ectothermic physiology, and high degree of interaction with the physical environment, tick life cycles are sensitive to changes in climate and weather conditions (Sonenshine and Roe 2013). Prior research has demonstrated that temperature and moisture strongly influence tick mortality, development, and host-seeking abilities (reviewed in

109 Ostfeld and Brunner 2015, Ogden and Lindsay 2016). In particular, both low and high

110 temperatures decrease *I. scapularis* and *I. pacificus* survival and host-seeking activity (Lindsay et

111 al. 1995, Vandyk et al. 1996, Padgett and Lane 2001). Further, cool temperatures prolong tick

112 development and increase generation times, leading to greater proportional mortality before

113 reproduction (Peavey and Lane 1996, Ogden et al. 2004, 2006). Rainfall and moisture

114 availability also influence host-seeking activity in nonlinear ways. Low humidity exposure

115 substantially increases tick mortality and inhibits host-seeking activity (Stafford 1994, Lane et al.

116 1995, Vail and Smith 1998, Schulze et al. 2001, Rodgers et al. 2007, Nieto et al. 2010, Ginsberg

117 et al. 2017, MacDonald et al. 2019b). To avoid desiccating conditions, Ixodid ticks often modify

118 their questing behavior to remain closer to the moist vegetative surface, or return frequently to

119 rehydrate, both of which decrease the probability of obtaining a blood meal and thereby limiting

120 survival and reproduction (Randolph and Storey 1999, Prusinski et al. 2006, Sonenshine and Roe

121 2013, Arsnoe et al. 2015, McClure and Diuk-Wasser 2019). However, heavy rainfall may also

122 directly impede tick host-seeking (Randolph 1997). Given these physiological relationships,

123 temperature and precipitation are important predictors of these tick species' latitudinal and

124 altitudinal range limits (McEnroe 1977, Estrada-Peña 2002, Brownstein et al. 2003, Ogden et al.

125 2005, Leighton et al. 2012, Berger et al. 2014, Eisen et al. 2016, Hahn et al. 2016), and

126 northward range expansion of *I. scapularis* has been associated with warming temperature

127 (Ogden et al. 2014b, Clow et al. 2017b, 2017a).

128   Yet despite well-known physiological relationships between specific climate variables

129 and aspects of tick biology, and strong evidence of relationships between climate and tick range

130 limits, it remains unclear how these effects translate into Lyme disease incidence - the outcome

131 of interest to public health - and how broadly they apply across biogeographically distinct US

132 regions. However, associations between climate and Lyme disease incidence are difficult to

133 measure given the influence of many non-climate factors such as changing physician awareness,

134 host movement, and human behavior (Morshed et al. 2006, Randolph 2010, Ostfeld and Brunner

135 2015, Kilpatrick et al. 2017, Scott and Scott 2018). A handful of prior studies have attempted to

136 isolate the effect of climate on incidence, but have been limited in geographic or temporal scope,

137 and/or not controlled for confounding drivers of incidence, leading to conflicting results about

138 the role of climate change on transmission (Subak 2003, McCabe and Bunnell 2004, Schauber et

139   al. 2005, Burtis et al. 2016, Dumic and Severnini 2018). As a result, our ability to predict effects

140   of future climate change on Lyme disease incidence remains limited.

141   Here, we leverage an 18-year county-level Lyme disease case reporting dataset and

142   explicitly control for other drivers of disease burden to ask: How has interannual variation in

143   climate conditions contributed to past changes in Lyme disease incidence across distinct US

144   regions? We include climate variables capturing changes in temperature and precipitation

145   conditions and investigate how relationships between climate and Lyme disease outcomes vary

146   across different regions of the US (i.e., the Northeast, Midwest, Southeast, Southwest, Pacific

147   Southwest, and Pacific). We hypothesize that: a) warmer temperatures in northern regions and b)

148   spring precipitation in all regions promote tick survival and therefore increase Lyme disease

149   incidence, while c) hot, dry conditions during the questing period decrease tick host-seeking

150   activity, survival and disease incidence. To avoid drawing spurious conclusions about the effects

151   of climate, we analyze the effects of other known and potential drivers of disease incidence such

152   as changing forest cover, public awareness of tick-borne disease, and health-seeking behavior,

153   and use a statistical approach that explicitly accounts for unobserved heterogeneity in disease

154   incidence between counties and years. We then use these modeled, regionally-specific

155   relationships between climate and Lyme disease burden to investigate projected changes in US

156   Lyme disease incidence under future climate scenarios. We report the projected change in Lyme

157   disease incidence for individual US regions in 2040 – 2050 and 2090 – 2100 relative to

158   hindcasted 2010 – 2020 levels under two potential climate scenarios: RCP8.5, which reflects the

159   upper range of the literature on emissions, and RCP4.5, which reflects a moderate mitigation

160   scenario (Hayhoe et al. 2017).

161

Materials and Methods

Lyme disease case data

164   We obtained annual, county-level reports of Lyme disease cases spanning from 2000 to 2017

165   from the US Centers for Disease Control and Prevention (CDC) (see Supporting Information).

166   These disease case data provide the most spatially-resolved, publicly available surveillance data

167   in the US. Raw case counts were converted to incidence using annual county population sizes

168   from the US Census Bureau (USCB) and were expressed in cases per 100,000 people.

Climate data

An overwhelming number of climate variables, such as the mean, range, and maximum or minimum temperature or precipitation at different time scales, could conceivably affect Lyme disease transmission. To reduce the probability of identifying significant but spurious relationships between climate and incidence, we limited the variables considered here to: average winter temperature lagged 1.5 years; average spring precipitation; the number of hot, dry days in May – July (the nymphal tick questing period); cumulative average temperature; total annual precipitation; daily temperature variability; and daily precipitation variability (Table 1). These variables have either been previously associated with variation in Lyme disease incidence, tick range limits or abundance, or, in the case of daily temperature and precipitation variability, are grounded in physiological relationships between climate and tick life history but have not been previously tested. In particular, interannual variation in Lyme disease incidence in endemic regions has been positively associated with lagged average winter temperature (Subak 2003), average spring precipitation (McCabe and Bunnell 2004), and negatively associated with the number of hot, dry days in May – July (Burtis et al. 2016). A measure of cumulative annual temperature (degree days > 0°C) has been associated with *I. scapularis* population establishment and abundance (Jones and Kitron 2000, Ogden et al. 2004, 2006, Clow et al. 2017b), and cumulative annual precipitation has been associated with larval tick abundance (Jones and Kitron 2000). Frequent variation in temperature can decrease tick survival due to the energetic costs of adapting to changing conditions (Gigon 1985, Herrmann and Gern 2013), thus daily temperature and precipitation variability were included here to explore whether this effect scaled to affect transmission risk. Details about how these variables were calculated and further justification for their biological relevance are listed in Table 1.

For past climate conditions, we obtained daily, county-level average temperature and total precipitation data from the National Oceanic and Atmospheric Administration (NOAA) weather stations accessed via the CDC's Wide-ranging Online Data for Epidemiological Research (WONDER) database. To estimate future climate variables, we used NASA Goddard Institute for Space Studies CMIP5 data on modeled temperature and precipitation (Schmidt et al. 2014). Specifically, we obtained estimates of daily near-surface air temperature and precipitation through 2100 under the upper climate change scenario (RCP8.5) and a moderate climate change scenario (RCP4.5) (van Vuuren et al. 2011, Taylor et al. 2012). These climate scenarios are

200   relatively similar in the radiative forcing levels assumed through 2050 but diverge substantially

201   in the latter half of the century. Climate estimates from these two scenarios are provided at a 2° x

202   2.5° resolution; values were then ascribed to counties based on county latitude and longitude (see

203   Figure S1). Mean values for hindcasted and projected climate variables for each region are listed

204   in Table S1.

205

206   **Awareness data**

207   We controlled for variation in public awareness of ticks and Lyme disease using data from

208   Google trends on the frequency of "ticks" as a search term. We obtained data on "ticks" search

209   frequency, normalized for a given location and year, for 2004 (the first year the data were

210   available) to 2017. We also initially used "tick bite", and "Lyme disease" as search terms, but

211   found that these generated nearly identical coefficient estimates, thus we proceeded to use only

212   the "ticks" search term as a predictor. Search frequency data were aggregated at the designated

213   market area (DMA), the smallest spatial scale available. Search frequency values for a given

214   DMA, which contained an average of 14 counties, were applied equally to all counties therein.

215   We used a 1-year lagged version of the tick search variable, as awareness of tick-borne disease is

216   likely endogenous to incidence (i.e., higher Lyme disease incidence likely contributes to higher

217   tick search frequency and awareness) and using predetermined values reduces endogeneity

218   concerns (Bascle 2008).

219

220   **Health-seeking behavior data**

221   We explicitly controlled for variation in health-seeking behavior, previously posited as a driver

222   of Lyme disease reporting (Armstrong et al. 2001, Wilking and Stark 2014) by including health

223   insurance coverage and poverty as potential predictors. Given the logistical and financial

224   challenges in obtaining a Lyme disease diagnosis and treatment (Johnson et al. 2011, Adrion et

225   al. 2015), access to health care services may play a role in whether a Lyme disease case is

226   identified and reported. We obtained data on health insurance coverage, defined as the percent of

227   county residents with any form of health insurance coverage in a given year, for 2005 to 2017

228   from USCB's Small Area Health Insurance Estimates (SAHIE) program. We obtained data on

229   poverty, defined as the percent of county residents living in poverty in a given year, for 2000 to

230   2017 from the USCB.

231

Land cover data

233 We included two land cover variables putatively associated with higher tick-borne disease risk:

234 the percent forest in a given county and year, and the percent mixed development (Brownstein et

235 al. 2005b, Dister and Fish 1997, Frank et al. 1998, Glass et al. 1995, Killilea et al. 2008,

236 MacDonald et al. 2019a). We calculated these variables using 30-m resolution land cover data

237 from the US Geological Survey (USGS) National Land Cover Database (NLCD) (Yang et al.

238 2018). Percent forest included any deciduous, evergreen, or mixed forest. Mixed development

239 was defined as areas with a mixture of constructed materials and vegetation, including lawn

240 grasses, parks, golf courses, and vegetation planted in developed settings. We calculated county-

241 level values of these land cover variables for 2001, 2004, 2006, 2008, 2011, 2013, and 2016 as

242 these are the only years the NLCD dataset is currently available.

243 To estimate future land cover variables, we used land cover projections generated by the

244 USGS Earth Resources Observation and Science Center (EROS) using the IPCC Special Report

245 on Emissions Scenarios (SRES) (Sohl et al. 2014). Although newer socioeconomic pathways

246 have recently been developed (i.e., the "Shared Socioeconomic Pathways"), these scenarios have

247 not yet been incorporated into US land cover projections (Sohl 2019). We used modeled land

248 cover data under SRES B1, which reflects lower urban development, to align with the moderate

249 climate change scenario (RCP4.5), and SRES A1B, which reflects higher urban development and

250 conversion of natural lands, to align with the upper climate change scenario (RCP8.5)

251 (Nakicenovic et al. 2000, Rogelj et al. 2012, Sohl et al. 2014). Using these data, we again

252 calculated annual, county-level values of percent forest cover and mixed development for 2040 –

253 2050 and 2090 – 2100. However, as the 'mixed development' land cover class was not included

254 in the projected data, we instead used the 'mechanically disturbed' public or private land cover

255 class (see Supporting Information).

256

Regional divisions

258 Given the large variation in climatic conditions across the US, as well as variation in ecological

259 dynamics of tick-borne diseases such as tick species identity, tick densities, tick questing

260 behavior, and host community composition (Eisen et al. 2016, Kilpatrick et al. 2017, Ostfeld

261 1997, Salkeld and Lane 2010), we examined regional differences in climate-disease

262   relationships. We used the US Fish & Wildlife Service regional boundaries to divide the US into

263   the following seven regions for analysis: Northeast, Midwest, Mountain Prairie, Pacific, Pacific

264   Southwest, Southwest, and Southeast (Figure 1). These regional divisions were selected as they

265   roughly correspond to genetic structuring of *I. scapularis* and *I. pacificus* (Kain et al. 1997, 1999,

266   Humphrey et al. 2010) and are likely distinct in environmental conditions and resources (Ricketts

267   et al. 1999, Smith et al. 2018). These regional divisions are also similar to the nine 'climatically

268   consistent' regions within the contiguous US identified by NOAA (Karl and Kloss 1984) but

269   preserve larger regions in the South and Midwest to obtain higher power in the analysis. Further,

270   each region contains only one vector species: *I. scapularis* in the Northeast, Midwest, Southeast,

271   and Southwest, and *I. pacificus* in the Pacific and Pacific Southwest (Dennis et al. 1998). As

272   neither species has an established presence in the Mountain Prairie, this region was removed

273   from the analysis. Regional descriptions, including the population size (as of 2017), the number

274   of counties, and the average climate conditions, are provided in Table S2.

275

276   **Statistical analysis**

277   We used a least squares dummy variable (termed "fixed-effects" in econometrics) regression

278   approach to estimate changes in Lyme disease incidence using repeated observations of the same

279   groups (counties) from 2000 – 2017 (Larsen et al. 2019). This class of statistical approaches has

280   been developed to isolate potential causal relationships in the absence of randomized

281   experiments where such experiments are not feasible (Larsen et al. 2019, MacDonald and

282   Mordecai 2019). We included 'county' and 'year' dummy variables to control for any

283   unobserved heterogeneity that may influence reported Lyme disease incidence in a particular

284   county across all years (e.g., geographic features, number of health care providers), or influence

285   Lyme disease in all counties in a given year (e.g., changes in disease case definition),

286   respectively. All counties (n = 2,232) for which there were complete data on Lyme disease cases,

287   climate, and other predictors were included.

288   To account for regional variation in the predictors of tick-borne disease incidence

289   (Wimberly et al. 2008, Raghavan et al. 2014), we ran separate models for each US region (see

290   Methods: Regional divisions). We used stepwise variable selection, in which variables were

291   added if they reduced model Akaike information criterion (AIC) by two or more, to identify the

292   climate, land cover, and non-ecological predictors that best explained Lyme disease incidence in

293   each region (Yamashita et al. 2007, Zhang 2016). We assessed the multicollinearity of these

294   models by calculating the variance inflation factor (VIF). No predictors had VIF values greater

295   than 10 after the stepwise variable selection procedure, thus we did not remove any variables

296   from the final models due to high collinearity (Hair et al. 2014).

297   We accounted for spatial and temporal autocorrelation of model errors by using cluster-

298   robust standard errors. This nonparametric approach accounts for arbitrary forms of

299   autocorrelation within a defined "cluster" to avoid misleadingly small standard errors and test

300   statistics (Cameron and Miller 2015). We specified clusters as US Agricultural Statistics

301   Districts (ASDs), which contain on average 9.9 ± 5.2 counties. These districts contain contiguous

302   counties grouped by similarities in soil type, terrain, and climate such that each district is more

303   homogenous with respect to these characteristics than the state as a whole (USDA 2018).

304   Accounting for spatial and temporal correlation in this way may help to account for ecological

305   similarities between neighboring counties not captured in the climate and land cover predictors.

306   Along these lines, ASDs have previously been used to account for spatial autocorrelation when

307   investigating relationships between forest fragmentation and Lyme disease incidence at the

308   county-level (MacDonald et al. 2019a). When reporting on the significance of a predictor, we

309   use standard errors and p-values calculated using this correction. To ensure our results were

310   robust to cluster specification, we repeated the model runs using county as the cluster unit (Table

311   S3). All analyses were conducted in R version 3.6 (R Core Team 2017)

312   To capture any nonlinear relationships between climate predictors and Lyme disease

313   incidence, we generated models using linear and quadratic versions of the climate variables as

314   potential predictors. Specifically, we used the stepwise variable selection approach starting with

315   linear and quadratic versions of each climate variable to determine the best fit model for each

316   region. We compare model accuracy and the output of these models to those using only linear

317   versions of climate predictors to assess the sensitivity of our results to the functional form of

318   climate-disease relationships (see Methods: Model validation).

319

320   **Lyme disease projections**

321   We projected Lyme disease incidence using the climate and land cover variables included in the

322   best fit model for each region as well as a county dummy variable. Tick search frequency,

323   poverty, and health insurance coverage were not included because annual, county-level

324   projections for these variables are unavailable. Using these models, we obtained regional

325   estimates for Lyme disease incidence under the upper and moderate climate change scenarios

326   (RCP8.5 and RCP4.5) for 2040 – 2050 and 2090 – 2100. We calculated county-level changes in

327   Lyme disease incidence by subtracting modeled incidence for 2010 – 2020 from projected

328   incidence. Using modeled incidence for 2010 – 2020, rather than true case data for the years it

329   was available, allowed for more direct comparisons between prior and projected cases because

330   these estimates were made using the same climate and land cover data.

331   We converted projected Lyme disease incidence to cases under two differing assumptions

332   about county population sizes. In the first calculation, we account for projected population

333   growth by using county-level population projections under the Shared Socioeconomic Pathway

334   "Middle of the Road" scenario (SSP2) as generated by Hauer 2019 (Samir and Lutz 2017). In the

335   second, we assume that county population sizes remained the same as those in 2017, the last year

336   of available county-level Lyme disease case reports. We focus our results and discussion on the

337   projections made using population size projections, but compare results from these two

338   approaches to ensure that changes in projected Lyme disease case counts resulted from predicted

339   changes in incidence rather than projected population growth or decline. We report point

340   estimates and 95% prediction intervals when discussing projected changes in Lyme disease case

341   counts.

342

343   **Model validation**

344   To evaluate predictive model accuracy, we compared hindcasted Lyme disease incidence under

345   both emissions scenarios to observed values for 2008 – 2017 (Judge et al. 1985, Clark et al.

346   2001). We compared model accuracy under varying model specifications to check the robustness

347   of the climate-disease relationships. In the first specification, each regional model contained the

348   predictors (climate, land cover, and non-ecological variables) determined through variable

349   selection (see Methods: Statistical analysis) as well as county and year dummy variables. In the

350   second specification, each regional model contained the same predictors as in the first

351   specification, but only linear versions of the climate predictors were included. This is to assess

352   the sensitivity of our results to the functional form of climate-disease relationships. Under the

353   third specification, regional models contained the same climate and non-climate predictors as in

354   the first specification but no dummy variables. Under the fourth specification, regional models

355   contained all possible climate and non-climate variables, and the county and year dummy

356   variables. Using each of these specifications, we created models of Lyme disease incidence on a

357   training dataset containing a randomly selected 75% subset of counties and years and used the

358   withheld 25% of observations for validation (Hijmans 2012, Caldwell et al. 2016). To evaluate

359   the performance of each model specification, we calculated the root-mean-square error (RMSE)

360   and correlation coefficient between projected and observed Lyme disease incidence for a given

361   county and year between 2008 – 2017 (the years with complete data for all predictors) for each

362   regional model. We also compared estimated average annual incidence to observed average

363   annual incidence for each model specification and each region. We used the modeled climate and

364   land cover data when hindcasting as these datasets were used for Lyme disease projections.

365

Results

Climate and Lyme disease incidence

368   At least one climate variable was included in the best fit model of Lyme disease incidence for all

369   US regions with vector species present (Table 2). However, the specific climate variable(s)

370   included in the model varied between regions and were often not significant predictors of

371   incidence. As hypothesized, cumulative temperature was a significant, positive predictor in the

372   Northeast, while the number of hot, dry days in May - July was a significant, negative predictor

373   in this region (Table 2). Hot, dry days was also a significant, negative predictor in the Midwest.

374   In the Southeast, daily temperature variability was a significant, positive predictor of incidence.

375   In all other regions, the temperature and/or precipitation variables included in the best fit models

376   were not statistically significant predictors. Further, for all regions, the climate predictors

377   explained relatively little of the variation in Lyme disease incidence compared to the county

378   dummy variables (Table 2). In many cases, quadratic versions of climate predictors were

379   included in the best fit model for a particular region, indicating nonlinearity in climate-disease

380   relationships (Table 2). For example, the number of hot, dry days, total annual precipitation, and

381   temperature variability were all nonlinear predictors in the best fit model for the Northeast.

382

Non-climate predictors and Lyme disease incidence

384   For all regions, the best fit model of Lyme disease incidence included the 1-year lagged tick

385   search frequency as well one health-seeking predictor and/or a land cover variable (Table 2).

386　Lagged tick search frequency was a significant, positive predictor in the Northeast, and had

387　regionally variable, and non-significant effects in other regions. Poverty was negatively

388　associated with Lyme disease incidence in the Northeast, and positively associated with

389　incidence in the Midwest and Southwest, but was not a significant predictor in any of these

390　models. Health insurance coverage was a non-significant, negative predictor of Lyme disease in

391　the Southeast. Forest cover was included in all regional models except the Southwest, but had

392　regionally variable effects and was only a significant predictor in the Pacific. Mixed

393　development cover was a positive predictor in the Southeast and Southwest, but only significant

394　in the Southeast. The above non-climate predictors were included in each regional model of

395　incidence along with county and year dummy variables. The majority of the variation in

396　incidence for each region was explained by the county dummy variable (Table 2), indicating that

397　there was a great deal of unobserved county-level heterogeneity driving Lyme disease incidence

398　that was captured by the dummy variables. However, the estimated effect sizes of the predictors

399　are the marginal effects of deviations from county- and year-means, meaning the total effect of a

400　given variable, such as forest cover, may be larger if much of the variation is captured by the

401　county fixed effects.

402

403　**Model Validation**

404　Under the main model specification, hindcasted Lyme disease incidence matched the observed

405　values with reasonable accuracy in the high incidence regions (Table 3 and Figure S1). In the

406　Northeast and Midwest, the correlations between estimated Lyme disease incidence for a given

407　county and year and the observed incidence were 0.85 and 0.90, respectively. Model accuracy

408　was lower in the Pacific, Pacific Southwest, Southwest, and Southeast, where incidence is much

409　lower (r = 0.40, 0.26, 0.07, 0.32, respectively). However, the estimated annual average Lyme

410　disease incidence (i.e., average incidence for a given region between 2008 – 2017) closely

411　matched the observed annual average for all regions (Table 3). For each region, the estimated

412　incidence was within 13% of the observed incidence, and was within 5% for the Northeast

413　specifically.

414　　　　Model accuracy also varied across the four model specifications (Table 3). In particular,

415　model specifications with dummy variables outperformed (i.e., lower RMSE, higher correlation

416　coefficients) those without. Models including only linear versions of climate predictors (i.e.,

417 model specification two) along with non-climate and dummy variables performed similarly to

418 the main model specification but with slightly lower correlation coefficients and higher RMSE in

419 the Northeast and Midwest, where the majority of cases occur. Coefficient estimates and Lyme

420 disease projections using this model specification are shown in Tables S4 and S5. Models

421 including all potential climate and non-climate predictors along with dummy variables had

422 similar accuracy to the main model specification and model specification two (Table 3). The

423 simpler, variable selection-based model specification using nonlinear climate predictors where

424 selected was thus used for the remaining analysis to minimize overfitting and decrease

425 transferability concerns (Allen and Fildes 2001, Wenger et al. 2011, Wenger and Olden 2012),

426 and to achieve the greatest accuracy in high Lyme disease incidence regions.

427

428 **Projected Lyme disease incidence**

429 Under the upper climate change scenario (RCP8.5), the number of Lyme disease cases in the

430 Northeast is projected to increase by 23,619 ± 21,607 by 2040 – 2050 and 61,776 ± 27,578 by

431 2090 – 2100 (Figures 2 and 3, Table 4). Non-significant decreases in the Midwest and increases

432 in the Southeast were also projected under this scenario, and minimal, non-significant changes

433 were projected for other regions (Table 4). By contrast, under the moderate climate change

434 scenario (RCP4.5), no regions were projected to significantly increase or decrease. Non-

435 significant increases in the Midwest, and non-significant increases or decreases, depending on

436 the decade, were projected for the Northeast, with minimal changes elsewhere. Given the

437 regionally variable projections and the large prediction intervals around all point estimates, total

438 US Lyme disease incidence is not projected to change significantly under either climate scenario

439 by 2040 – 2050 or 2090 – 2100 (Table 4). These results indicate that future changes in US Lyme

440 disease burden are highly uncertain, vary strongly by region, and will depend on the degree of

441 future climate change.

442 These Lyme disease projections were qualitatively similar to those generated using only

443 linear versions of the climate variables (Table S5). Under this model specification (model

444 specification two, see Methods: Model validation), the number of Lyme disease cases in the

445 Northeast is projected to increase under the upper climate change scenario (21,467 ± 21,354 by

446 2040 – 2050 and 42,538 ± 24,129 by 2090 – 2100), but not under the moderate climate scenario.

447 Non-significant decreases and increases in the Midwest were projected for the upper and

448   moderate climate scenario, respectively, and non-significant changes in the US as a whole were

449   projected under both scenarios and time periods. These results are all consistent with those

450   generated under the main model specification, indicating that our projections are generally robust

451   to the functional form of climate-disease relationships specified in the model. The one qualitative

452   difference in results is the significant increase in cases in the Southeast under the upper climate

453   change scenario (1,522 ± 1,213 by 2040 – 2050 and 3,460 ± 1,736 by 2090 – 2100) under model

454   specification two, which was marginally non-significant under the main model specification.

455   Lyme disease case projections made using county-level population size projections were

456   similar to those using constant (i.e., 2017) population sizes. In particular, large but uncertain

457   increases in Lyme diseases cases were still projected for the Northeast under the upper climate

458   change scenario (18,885 ± 19,509 by 2040 – 2050 and 40,320 ± 21,886 by 2090 – 2100) when

459   assuming constant population sizes. This indicates that our results are generally robust to

460   population size assumptions and are not solely driven by projected changes in human

461   demography. However, because population growth is projected for the Northeast (Hauer et al.

462   2019; Table S7), projections made assuming constant population sizes are smaller (but not

463   significantly) than those using projected population sizes.

464

Discussion

466   Given the increasing rate of vector-borne disease emergence and re-emergence in recent decades,

467   including Zika in Central and South America and tick-borne encephalitis in Europe, identifying

468   the environmental drivers of vector-borne disease transmission has been a major research theme

469   (Rogers and Randolph 2006, Kilpatrick and Randolph 2012, Lafferty and Mordecai 2016, Swei

470   et al. 2019). Extensive prior research indicates that temperature and moisture conditions can

471   impact vector life cycles, activity patterns, abundance, and range limits (reviewed in Ogden and

472   Lindsay 2016). Yet despite clear relationships between specific features of climate and aspects of

473   vector life cycles and biology, identifying how these relationships translate to affect disease

474   incidence has remained challenging. Here we use 18 years of disease and climate data in a panel

475   data statistical modeling approach to identify the impacts of climate change on human Lyme

476   disease incidence across biogeographically distinct US regions. We find that climate was a

477   predictor of interannual variation in Lyme disease incidence in all US regions with established

478   vector species (Northeast, Midwest, Pacific, Pacific Southwest, Southwest, and Southeast), even

479   after controlling for potentially confounding factors and spurious relationships spatially and

480   temporally. However, the specific climate variable(s) that best predicted burdens varied between

481   regions and had highly variable effect sizes and often nonlinear relationships with incidence.

482   While these results underscore the complexity of climate-Lyme disease relationships, the specific

483   associations observed here tended to reflect known relationships between climate and the life

484   histories of the US vectors of Lyme disease, *I. scapularis* and *I. pacificus*.

485   The strongest climate-disease association detected was between warming annual

486   temperatures and increasing Lyme disease incidence in the Northeast. Previous studies have

487   found that warming year-round temperatures at high latitudes contribute to more rapid tick

488   development rates, increased survival, and *I. scapularis* range expansion (Clow et al. 2017a,

489   Leighton et al. 2012, Lindsay et al. 1995, Ogden et al. 2004, Rand et al. 2004). This suggests

490   warmer temperatures near the ticks' northern range limit would promote Lyme disease

491   transmission – an expectation empirically supported in this study. We also found a significant

492   negative association between hot, dry conditions during the nymphal questing period (May –

493   July) and incidence in the Northeast and Midwest. Prior studies indicate that desiccating

494   conditions reduce tick questing activity, which can lead to decreased contact rates with larger

495   vertebrate hosts, including humans (Randolph and Storey 1999, Prusinski et al. 2006, Sonenshine

496   and Roe 2013). Further, Burtis et al. 2016 found the number of hot, dry days during this period

497   was significantly negatively associated with *I. scapularis* questing density as well as Lyme

498   disease incidence in the Hudson Valley, Southern New England, and northern New Jersey. Our

499   work thus provides evidence that these prior relationships between desiccating conditions and

500   tick questing behavior scale to incidence across the Northeast and Midwest. That this

501   relationship was not observed or significant in the Southeast or Southwest is also consistent with

502   prior evidence of differing questing behavior in northern and southern *I. scapularis* nymphs.

503   Northern *I. scapularis* nymphs are much more likely to quest above the leaf litter, while southern

504   *I. scapularis* nymphs primarily use habitats below the vegetative surface (Arsnoe et al. 2015). As

505   this different questing behavior buffers southern *I. scapularis* from desiccating conditions,

506   variation in the number of hot, dry days is less likely to impact tick-host contact rates and disease

507   transmission here. Similar differences in questing behavior have been demonstrated between

508   northern and southern population of *I. pacificus* (Lane et al. 2013, MacDonald and Briggs 2016),

509   but we find no significant relationship between hot, dry days and incidence in the Pacific,

510   potentially because low Lyme disease incidence in this region reduces the power to detect effects

511   of variation in climate on incidence. Although we did find the expected negative relationship

512   between hot, dry days and incidence in the Northeast and Midwest, we did not detect the

513   hypothesized positive relationship between spring precipitation and Lyme disease incidence in

514   any region. We did find a positive association in the Northeast and Pacific Southwest, but the

515   association was not significant, and it was negative (but non-significant) in the Midwest and

516   Southwest. This may be due to counteracting effects of precipitation on human behavior leading

517   to reduced tick-human contact rates (Jaenson et al. 2012), independent of effects of precipitation

518   on tick host-seeking suitability.

519   The associations between climate conditions and Lyme disease incidence found here

520   were detected while rigorously controlling for non-climate predictors of disease as well as

521   unobserved predictors that covary with climate at the county and year levels. In particular, we

522   explicitly controlled for variation in human awareness of ticks, land use and land cover

523   characteristics, proxies for health-seeking behavior, and other unobserved heterogeneity between

524   US counties and years in our modeling approach. Increasing tick awareness, as determined by

525   the frequency of tick-related Google searches, was generally positively associated with Lyme

526   disease incidence, while land cover and health-seeking behavior predictors had regionally

527   variable relationships. By controlling for these effects, we provide strong evidence that the

528   positive association between warming temperatures and Lyme disease incidence in the Northeast

529   found in this study is not simply driven by increasing human awareness of tick-borne disease,

530   temporal trends, or other concurrent changes as has been previously suggested (Morshed et al.

531   2006, Randolph 2010, Scott and Scott 2018). Further, the total effects of climate and land use

532   predictors may be larger than those estimated here, because these ecological predictors may

533   underlie some of the variation included in the county and year dummy variables.

534   While our statistical models included both climate and non-climate predictors of Lyme

535   disease incidence, model accuracy varied widely between regions. Most notably, model accuracy

536   was substantially greater for endemic regions (Northeast and Midwest), compared to low

537   incidence (non-endemic) regions (Pacific, Pacific Southwest, Southwest, and Southeast)

538   (Ciesielski et al. 1988). The relatively poor predictive accuracy in non-endemic regions could be

539   due to higher misdiagnosis rates and/or higher travel-associated Lyme disease transmission

540   (Eldin and Parola 2018, Parola and Paddock 2018) decoupling the relationship between local

541   conditions and disease. However, evidence suggests that most Lyme disease transmission occurs

542   in the peri-domestic environment, in which the county of transmission and reporting are likely to

543   be the same (Falco and Fish 1988, Maupin et al. 1991, Jackson et al. 2006, Connally et al. 2009).

544   The lower predictive accuracy in these regions more likely reflects a lack of sufficient annual

545   variation in Lyme disease incidence needed to detect effects of climate in these regions above

546   and beyond the county and year fixed effects, and/or weaker effects of climate conditions on

547   Lyme disease transmission relative to confounding drivers not included in our model such as

548   host movement and community composition. In contrast, the largest effect of climate on disease

549   transmission is expected at the edges of the climate suitability for transmission (Githeko et al.

550   2000). As portions of the Northeast and Midwest are near the *I. scapularis* northern range limit,

551   the higher model accuracy here likely indicates stronger climate – Lyme disease relationships.

552   Supporting this assertion, the climate predictors explained a relatively larger proportion of the

553   variation in incidence in these regions.

554   Our Lyme disease projections, made using regionally-specific incidence models and

555   projected climate and land cover data, suggest that climate change may lead to substantial

556   increases in incidence in coming decades, but that these increases are largely concentrated in the

557   Northeast, are highly uncertain, and depend upon the magnitude of climate change. In particular,

558   under the upper climate change scenario (RCP8.5), Lyme disease cases in the Northeast are

559   projected to increase by $23{,}619 \pm 21{,}607$ by 2040 – 2050 and $61{,}776 \pm 27{,}578$ by 2090 – 2100

560   (Table 4). However, increases are not projected in the Northeast under the moderate climate

561   change scenario (RCP4.5), nor for any other region under either scenario. Large increases in the

562   Midwest under less severe warming are possible, as are large increases in total US cases under

563   more severe warming, but these projections are non-significant. While the significant increase in

564   Lyme disease cases projected for the Northeast under RCP8.5 was robust to alternative model

565   specifications and assumptions about county-level population growth, the large prediction

566   intervals around our point estimates for this region and all others indicate a wide range of

567   potential disease outcomes under climate change.

568   These results indicate that climate change will likely contribute to increasing Lyme

569   disease incidence in the Northeast, but the specific numerical projections should be interpreted

570   with caution. While significant increases were projected in the Northeast, many other factors

571 contribute to Lyme disease transmission including host movement and community composition,

572 and human avoidance behaviors (Ostfeld 1997, Brownstein et al. 2005b, Ogden et al. 2008,

573 Brinkerhoff et al. 2011, Larsen et al. 2014, Berry et al. 2018, MacDonald et al. 2019a).

574 Accordingly, we found that unobserved county-level heterogeneity, which would encompass

575 these factors, was a predominant driver of incidence in each of our regional models. Thus, while

576 climate may contribute to increasing Lyme disease incidence in northern regions, it may not be

577 the dominant driver of future changes in Lyme disease. Further, while we examined the effects

578 of two potential climate scenarios, uncertainty in these climate change projections was not

579 incorporated into our predictive models and would contribute additional uncertainty in Lyme

580 disease projections. Lastly, the projection models extrapolate from climate and disease

581 relationships observed in the previous 18 years, assuming that these relationships can be

582 extended to climate conditions not yet experienced. That is, we assume that the relationship

583 between cumulative temperature, for example, and Lyme disease incidence in a given region will

584 remain the same even as cumulative temperatures exceed prior values. This could generate

585 inaccurate projections for regions near current tick upper thermal limits such as the Southeast

586 and Southwest as further warming and drought here may reduce tick survival and host-seeking

587 suitability (Vail and Smith 1998, Randolph and Storey 1999, Schulze et al. 2001, Berger et al.

588 2014, MacDonald et al. 2020). Generating more accurate projections for these regions would

589 require experiments investigating effects of future temperatures on aspects of tick-borne disease

590 transmission.

591   Despite these limitations and the large uncertainty in our Lyme disease projections, our

592 results are consistent with a growing body of evidence linking increased Lyme disease risk with

593 climate warming (Brownstein et al. 2005a, Burtis et al. 2016, Clow et al. 2017b, Dumic and

594 Severnini 2018, Kilpatrick et al. 2017, Leighton et al. 2012, Ogden et al. 2008,2014b, Robinson

595 et al. 2015, Subak 2003, Tuite et al. 2013). Specifically, our finding of climate change-induced

596 increases in Lyme disease burden at higher latitudes, is consistent with prior studies projecting or

597 observing increasing *I. scapularis* habitat suitability and range expansion under climate warming

598 (Ogden et al. 2008, 2014a, McPherson et al. 2017). Similar range expansions have also been

599 projected and observed for *Ixodes ricinus*, the European Lyme disease vector, under climate

600 warming (Gray et al. 2009, Jaenson and Lindgren 2011, Lindgren et al. 2000, Porretta et al.

601 2013). Further, our finding that the projected changes in incidence depend on the degree of

602   future warming is also consistent with prior work. *I. scapularis* range expansion and population

603   growth, and the proportion of Eastern Canadians at risk for Lyme disease, are projected to be

604   higher under upper climate change scenarios than under mitigation scenarios (Leighton et al.

605   2012, McPherson et al. 2017). These results suggest that vector range expansions and future

606   Lyme disease burdens depend in part on climate policy actions.

607   More generally, our results are consistent with expectations from vector thermal biology

608   that suggest that warming temperatures generally increase transmission near the cold edge of a

609   vector's range limit, but may decrease or have variable effects elsewhere (Martens et al. 1995,

610   Ogden and Lindsay 2016, Lafferty and Mordecai 2016, Mordecai et al. 2019). For tick-borne

611   diseases, as for other vector-borne diseases, multiple temperature-sensitive traits combine to

612   influence transmission, including survival, development rates, and host-seeking (Randolph et al.

613   2002, Ogden et al. 2004, Randolph 2004, Ogden and Lindsay 2016, Ogden 2017). Nonlinear

614   effects of temperature on these traits typically leads to vector-borne disease transmission peaking

615   at intermediate temperatures and declining as temperatures approach lower and upper thermal

616   limits (Mordecai et al. 2019). This suggests that climate warming would most strongly increase

617   transmission near the lower thermal limits, such as in the Northeast, as was observed here. This

618   further suggests the effects of climate warming would differ in magnitude and direction

619   depending on the extent of warming, as seen in the Midwest region where non-significant

620   increases were projected under the moderate climate change scenario while decreases were

621   projected under the upper scenario. The theoretical expectations of nonlinear thermal responses

622   therefore help to explain some of the context-dependent effects of temperature found empirically

623   in this study.

624

Conclusions

626   We demonstrate that interannual variation in Lyme disease incidence is associated with climate

627   in all US regions with established vector species, independent of other drivers of disease risk and

628   excluding potentially spurious relationships with county- and year-specific variation. The

629   specific climate variable(s) associated with incidence and their effect sizes varied by region, but

630   the strongest climate-disease association observed was between warming temperatures and

631   increasing incidence in the Northeast. However, in all regions, climate explained less variation in

632   incidence than unobserved county-specific heterogeneity, highlighting that climate is one of

633   many factors influencing Lyme disease transmission. We project that future climate change

634   could substantially increase Lyme disease burden in the Northeast in coming decades under an

635   upper climate change scenario. Cases in the Northeast were not projected to increase under a

636   moderate climate change scenario, highlighting the potential for climate change mitigation to

637   protect human health by preventing further increases in Lyme disease incidence. However, the

638   projected effects in this region and all others are highly uncertain, indicating a wide range of

639   potential disease outcomes under climate change. Our projections provide an essential first step

640   in determining broad patterns of Lyme disease risk under climate change, but ongoing

641   surveillance efforts and mechanistic studies linking changes in vector ecology under climate

642   change to human disease incidence should be conducted to refine these risk assessments.

643

657

658   **Data Accessibility:**

659   All datasets used in this study are free and publicly available. These datasets can be found here:

660   https://github.com/lcouper/LymeDiseaseClimateChange, along with information about where

661   and when they were originally accessed.

662

References:

663 Adrion, E. R., J. Aucott, K. W. Lemke, and J. P. Weiner. 2015. Health care costs, utilization and
665   patterns of care following Lyme disease. PLOS ONE 10:e0116767.

666 Allen, P. G., and R. Fildes. 2001. Econometric Forecasting. Pages 303–362 *in* J. S. Armstrong,
667   editor. Principles of Forecasting. Springer US, Boston, MA.

668 Armstrong, P. M., L. R. Brunet, A. Spielman, and S. R. Telford III. 2001. Risk of Lyme disease:
669   perceptions of residents of a Lone Star tick-infested community. Bulletin of the World
670   Health Organization 79:916–925.

671 Arsnoe, I. M., G. J. Hickling, H. S. Ginsberg, R. McElreath, and J. I. Tsao. 2015. Different
672   populations of blacklegged tick nymphs exhibit differences in questing behavior that
673   have implications for human Lyme disease risk. PLOS ONE 10:e0127450.

674 Bascle, G. 2008. Controlling for endogeneity with instrumental variables in strategic
675   management research. Strategic Organization 6:285–327.

676 Berger, K. A., H. S. Ginsberg, K. D. Dugas, L. H. Hamel, and T. N. Mather. 2014. Adverse
677   moisture events predict seasonal abundance of Lyme disease vector ticks (Ixodes
678   scapularis). Parasites & Vectors 7:181.

679 Berry, K., J. Bayham, S. R. Meyer, and E. P. Fenichel. 2018. The allocation of time and risk of
680   Lyme: A case of ecosystem service income and substitution effects. Environmental and
681   Resource Economics 70:631–650.

682 Brinkerhoff, R. J., C. M. Folsom-O'Keefe, K. Tsao, and M. A. Diuk-Wasser. 2011. Do birds
683   affect Lyme disease risk? Range expansion of the vector-borne pathogen *Borrelia*
684   *burgdorferi*. Frontiers in Ecology and the Environment 9:103–110.

685 Brownstein, J. S., T. R. Holford, and D. Fish. 2003. A climate-based model predicts the spatial
686   distribution of the Lyme disease vector Ixodes scapularis in the United States.
687   Environmental Health Perspectives 111:1152–1157.

688 Brownstein, J. S., T. R. Holford, and D. Fish. 2005a. Effect of climate change on Lyme disease
689   risk in North America. EcoHealth 2:38–46.

690 Brownstein, J. S., D. K. Skelly, T. R. Holford, and D. Fish. 2005b. Forest fragmentation predicts
691   local scale heterogeneity of Lyme disease risk. Oecologia 146:469–475.

692   Burtis, J. C., P. Sullivan, T. Levi, K. Oggenfuss, T. J. Fahey, and R. S. Ostfeld. 2016. The impact
693   of temperature and precipitation on blacklegged tick activity and Lyme disease incidence
694   in endemic and emerging regions. Parasites & Vectors 9.

695   Caldwell, J., S. Heron, C. Eakin, and M. Donahue. 2016. Satellite SST-based coral disease
696   outbreak predictions for the Hawaiian archipelago. Remote Sensing 8:93.

697   Cameron, A. C., and D. L. Miller. 2015. A practitioner's guide to cluster-robust inference.
698   Journal of Human Resources 50:317–372.

699   Clark, J. S., S. R. Carpenter, M. Barber, S. Collins, A. Dobson, J. A. Foley, D. M. Lodge, M.
700   Pascual, R. Pielke, W. Pizer, C. Pringle, W. V. Reid, K. A. Rose, O. Sala, W. H.
701   Schlesinger, D. H. Wall, and D. Wear. 2001. Ecological forecasts: An emerging
702   imperative. Science 293:657–660.

703   Clow, K. M., P. A. Leighton, N. H. Ogden, L. R. Lindsay, P. Michel, D. L. Pearl, and C. M.
704   Jardine. 2017a. Northward range expansion of *Ixodes scapularis* evident over a short
705   timescale in Ontario, Canada. PLOS ONE 12:e0189393.

706   Clow, K. M., N. H. Ogden, L. R. Lindsay, P. Michel, D. L. Pearl, and C. M. Jardine. 2017b. The
707   influence of abiotic and biotic factors on the invasion of I*xodes scapularis* in Ontario,
708   Canada. Ticks and Tick-borne Diseases 8:554–563.

709   Dennis, D. T., T. S. Nekomoto, J. C. Victor, W. S. Paul, and J. Piesman. 1998. Reported
710   Distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the United
711   States. Journal of Medical Entomology 35:629–638.

712   Dister, S. W., and D. Fish. 1997. Landscape characterization of peridomestic risk for Lyme
713   disease using satellite imagery. Americal Journal of Tropical Medicine and Hygiene:6.

714   Dumic, I., and E. Severnini. 2018. "Ticking bomb": The impact of climate change on the
715   incidence of Lyme disease. 2018:5719081

716   Eisen, R. J., L. Eisen, N. H. Ogden, and C. B. Beard. 2016. Linkages of weather and climate with
717   *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae), enzootic transmission of
718   *Borrelia burgdorferi* and Lyme disease in North America. Journal of Medical
719   Entomology 53:250–261.

720   Estrada-Peña, A. 2002. Increasing habitat suitability in the United States for the tick that
721   transmits Lyme disease: a remote sensing approach. Environmental Health Perspectives
722   110:635–640.

723   Frank, D. H., D. Fish, and F. H. Moy. 1998. Landscape features associated with Lyme disease
724   risk in a suburban residential environment. Landscape Ecology 13:27–36.

725   Gigon, F. 1985. Biologie d'Ixodes ricinus L. sur le Plateau Suisse – une contribution à l'écologie
726   de ce vecteur. Université de Neuchâtel, Neuchâtel, Switzerland.

727   Ginsberg, H. S., M. Albert, L. Acevedo, M. C. Dyer, I. M. Arsnoe, J. I. Tsao, T. N. Mather, and
728   R. A. LeBrun. 2017. Environmental factors affecting survival of immature *Ixodes*
729   *scapularis* and implications for geographical distribution of Lyme disease: The
730   climate/behavior hypothesis. PLOS ONE 12:e0168723.

731   Glass, G. E., B. S. Schwartz, J. M. Morgan, D. T. Johnson, P. M. Noy, and E. Israel. 1995.
732   Environmental risk factors for Lyme disease identified with geographic information
733   systems. American Journal of Public Health 85:944–948.

734   González, C., O. Wang, S. E. Strutz, C. González-Salazar, V. Sánchez-Cordero, and S. Sarkar.
735   2010. Climate change and risk of Leishmaniasis in North America: Predictions from
736   ecological niche models of vector and reservoir species. PLoS Neglected Tropical
737   Diseases 4:e585.

738   Gray, J. S., H. Dautel, A. Estrada-Peña, O. Kahl, and E. Lindgren. 2009. Effects of climate
739   change on ticks and tick-borne diseases in Europe. Interdisciplinary Perspectives on
740   Infectious Diseases 2009:1–12.

741   Hahn, M. B., C. S. Jarnevich, A. J. Monaghan, and R. J. Eisen. 2016. Modeling the geographic
742   distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the contiguous
743   United States. Journal of Medical Entomology 53:1176–1191.

744   Hair, J. F., W. C. Black, B. Babin, and R. Anderson, editors. 2014. Multivariate data analysis.
745   Seventh edition. Pearson.

746   Hauer, M. E. 2019. Population projections for U.S. counties by age, sex, and race controlled to
747   shared socioeconomic pathway. Scientific Data 6.

748   Hayhoe, K., J. Edmonds, R. E. Kopp, A. N. LeGrande, B. M. Sanderson, M. F. Wehner, and D.
749   J. Wuebbles. 2017. 2017: Climate models, scenarios, and projections. Pages 133–160 *in*
750   D. J. Wuebbles, D. W. Fahey, K. A. Hibbard, D. J. Dokken, B. C. Stewart, and T. K.
751   Maycock, editors. Climate Science Special Report: Fourth National Climate Assessment,
752   Volume I. U.S. Global Change Research Program Washington, DC, USA.

753   Herrmann, C., and L. Gern. 2013. Survival of *Ixodes ricinus* (Acari: Ixodidae) nymphs under

754   cold conditions is negatively influenced by frequent temperature variations. Ticks and

755   Tick-borne Diseases 4:445–451.

756   Hii, Y. L., J. Rocklöv, N. Ng, C. S. Tang, F. Y. Pang, and R. Sauerborn. 2009. Climate

757   variability and increase in intensity and magnitude of dengue incidence in Singapore.

758   Global Health Action 2:2036.

759   Hijmans, R. J. 2012. Cross-validation of species distribution models: removing spatial sorting

760   bias and calibration with a null model. Ecology 93:679–688.

761   Humphrey, P. T., D. A. Caporale, and D. Brisson. 2010. Uncoordinated phylogeography of

762   *Borrelia burgdorferi* and its tick vector, *Ixodes scapularis*. Evolution 64:2653–2663.

763   Jaenson, T. G., D. G. Jaenson, L. Eisen, E. Petersson, and E. Lindgren. 2012. Changes in the

764   geographical distribution and abundance of the tick *Ixodes ricinus* during the past 30

765   years in Sweden. Parasites & Vectors 5:1–15.

766   Jaenson, T. G. T., and E. Lindgren. 2011. The range of *Ixodes ricinus* and the risk of contracting

767   Lyme borreliosis will increase northwards when the vegetation period becomes longer.

768   Ticks and Tick-borne Diseases 2:44–49.

769   Johnson, L., A. Aylward, and R. B. Stricker. 2011. Healthcare access and burden of care for

770   patients with Lyme disease: A large United States survey. Health Policy 102:64–71.

771   Jones, C. J., and U. D. Kitron. 2000. Populations of *Ixodes scapularis* (Acari: Ixodidae) are

772   modulated by drought at a Lyme disease focus in Illinois. Journal of Medical Entomology

773   37:408–415.

774   Judge, G., W. Griffiths, R. Carter, H. Lutkepohl, and T. Lee. 1985. The theory and practice of

775   econometrics. Wiley, New York.

776   Kain, D. E., F. A. H. Sperling, H. V. Daly, and R. S. Lane. 1999. Mitochondrial DNA sequence

777   variation in *Ixodes pacificus* (Acari: Ixodidae). Heredity 83:378–386.

778   Kain, D. E., F. A. H. Sperling, and R. S. Lane. 1997. Population genetic structure of *Ixodes*

779   *pacificus* (Acari: Ixodidae) using allozymes. Journal of Medical Entomology 34:441–

780   450.

781   Killilea, M. E., A. Swei, R. S. Lane, C. J. Briggs, and R. S. Ostfeld. 2008. Spatial Dynamics of

782   Lyme Disease: A Review. EcoHealth 5:167–195.

783   Kilpatrick, A. M., A. D. M. Dobson, T. Levi, D. J. Salkeld, A. Swei, H. S. Ginsberg, A.
784   Kjemtrup, K. A. Padgett, P. M. Jensen, D. Fish, N. H. Ogden, and M. A. Diuk-Wasser.
785   2017. Lyme disease ecology in a changing world: consensus, uncertainty and critical gaps
786   for improving control. Philosophical Transactions of the Royal Society B: Biological
787   Sciences 372:20160117.

788   Kilpatrick, A. M., and S. E. Randolph. 2012. Drivers, dynamics, and control of emerging vector-
789   borne zoonotic diseases. The Lancet 380:1946–1955.

790   Kurtenbach, K., K. Hanincová, J. I. Tsao, G. Margos, D. Fish, and N. H. Ogden. 2006.
791   Fundamental processes in the evolutionary ecology of Lyme borreliosis. Nature Reviews
792   Microbiology 4:660–669.

793   Lafferty, K. D., and E. A. Mordecai. 2016. The rise and fall of infectious disease in a warmer
794   world. F1000Research 5.

795   Lane, R. S., N. Fedorova, J. E. Kleinjan, and M. Maxwell. 2013. Eco-epidemiological factors
796   contributing to the low risk of human exposure to ixodid tick-borne borreliae in southern
797   California, USA. Ticks and Tick-borne Diseases 4:377–385.

798   Lane, R. S., J. E. Kleinjan, and G. B. Schoeler. 1995. Diel activity of nymphal *Dermacentor*
799   *occidentalis* and *Ixodes pacificus* (Acari: Ixodidae) in relation to meteorological factors
800   and host activity periods. Journal of Medical Entomology 32:290–299.

801   Larsen, A. E., A. J. MacDonald, and A. J. Plantinga. 2014. Lyme disease risk influences human
802   settlement in the wildland–urban interface: Evidence from a longitudinal analysis of
803   counties in the northeastern United States. The American Journal of Tropical Medicine
804   and Hygiene 91:747–755.

805   Larsen, A. E., K. Meng, and B. E. Kendall. 2019. Causal analysis in control-impact ecological
806   studies with observational data. Methods in Ecology and Evolution.

807   Leighton, P. A., J. K. Koffi, Y. Pelcat, L. R. Lindsay, and N. H. Ogden. 2012a. Predicting the
808   speed of tick invasion: an empirical model of range expansion for the Lyme disease
809   vector *Ixodes scapularis* in Canada. Journal of Applied Ecology 49:457–464.

810   Lindgren E, Tälleklint L, and Polfeldt T. 2000. Impact of climatic change on the northern
811   latitude limit and population density of the disease-transmitting European tick *Ixodes*
812   *ricinus*. Environmental Health Perspectives 108:119–123.

813   Lindsay, L. R., I. K. Barker, G. A. Surgeoner, S. A. McEwen, T. J. Gillespie, and J. T. Robinson.

814   1995. Survival and development of *Ixodes scapularis* (Acari: Ixodidae) under various

815   climatic conditions in Ontario, Canada. Journal of Medical Entomology 32:143–152.

816   Loevinsohn, M. E. 1994. Climatic warming and increased malaria incidence in Rwanda. The

817   Lancet 343:714–718.

818   MacDonald, A. J., and C. J. Briggs. 2016. Truncated seasonal activity patterns of the western

819   blacklegged tick (*Ixodes pacificus*) in central and southern California. Ticks and Tick-

820   borne Diseases 7:234–242.

821   MacDonald, A. J., A. E. Larsen, and A. J. Plantinga. 2019a. Missing the people for the trees:

822   Identifying coupled natural–human system feedbacks driving the ecology of Lyme

823   disease. Journal of Applied Ecology 56:354–364.

824   MacDonald, A. J., S. McComb, C. O'Neill, K. A. Padgett, and A. E. Larsen. 2020. Projected

825   climate and land use change alter western blacklegged tick phenology, seasonal host-

826   seeking suitability and human encounter risk in California. Global Change Biology

827   2020:1–16.

828   MacDonald, A. J., and E. A. Mordecai. 2019. Amazon deforestation drives malaria transmission,

829   and malaria burden reduces forest clearing. Proceedings of the National Academy of

830   Sciences 116:22212–22218.

831   MacDonald, A. J., C. O'Neill, M. H. Yoshimizu, K. A. Padgett, and A. E. Larsen. 2019b.

832   Tracking seasonal activity of the western blacklegged tick across California. Journal of

833   Applied Ecology 56:2562–2573.

834   Martens, W., T. Jetten, J. Rotmans, and L. Niessen. 1995. Climate change and vector-borne

835   diseases: A global modelling perspective. Global Environmental Change 5:195–209.

836   Mattingly, P. F. 1969. The biology of mosquito-borne disease. London: George Allen and Unwin

837   Ltd.

838   McCabe, G. J., and J. E. Bunnell. 2004. Precipitation and the occurrence of Lyme disease in the

839   northeastern United States. Vector-Borne and Zoonotic Diseases 4:143–148.

840   McClure, M., and M. A. Diuk-Wasser. 2019. Climate impacts on blacklegged tick host-seeking

841   behavior. International Journal for Parasitology 49:37–47.

842   McEnroe, W. D. 1977. Restriction of the species range of *Ixodes scapularis*, Say, in

843   Massachusetts by fall and winter temperature. Acarologia.

844　McPherson, M., A. García-García, F. J. Cuesta-Valero, H. Beltrami, P. Hansen-Ketchum, D.
845　　　　MacDougall, and N. H. Ogden. 2017. Expansion of the Lyme disease vector *Ixodes*
846　　　　*scapularis* in Canada inferred from CMIP5 climate projections. Environmental Health
847　　　　Perspectives 125:057008.

848　Mills, J. N., K. L. Gage, and A. S. Khan. 2010. Potential influence of climate change on vector-
849　　　　borne and zoonotic diseases: A review and proposed research plan. Environmental Health
850　　　　Perspectives 118:1507–1514.

851　Mordecai, E. A., J. M. Caldwell, M. K. Grossman, C. A. Lippi, L. R. Johnson, M. Neira, J. R.
852　　　　Rohr, S. J. Ryan, V. Savage, M. S. Shocket, R. Sippy, A. M. S. Ibarra, M. B. Thomas,
853　　　　and O. Villena. 2019. Thermal biology of mosquito-borne disease. Ecology Letters
854　　　　22:1690–1708.

855　Morshed, M. G., J. D. Scott, K. Fernando, G. Geddes, A. Mcnabb, S. Mak, and L. A. Durden.
856　　　　2006. Distribution and characterization of *Borrelia burgdorferi* isolates from I*xodes*
857　　　　*scapularis* and presence in mammalian hosts in Ontario, Canada. Journal of Medical
858　　　　Entomology 43:762–773.

859　Nakicenovic, N., J. Alcamo, A. Grubler, K. Riahi, R. A. Roehrl, H.-H. Rogner, and N. Victor.
860　　　　2000. Special Report on Emissions Scenarios (SRES), A Special Report of Working
861　　　　Group III of the Intergovernmental Panel on Climate Change. Cambridge University
862　　　　Press, Cambridge.

863　Nieto, N. C., E. A. Holmes, and J. E. Foley. 2010. Survival rates of immature *Ixodes pacificus*
864　　　　(Acari: Ixodidae) ticks estimated using field-placed enclosures. Journal of Vector
865　　　　Ecology 35:43–49.

866　Ogden, N. H. 2017. Climate change and vector-borne diseases of public health significance.
867　　　　FEMS Microbiology Letters 364.

868　Ogden, N. H., M. Bigras-Poulin, C. J. O'Callaghan, I. K. Barker, L. R. Lindsay, A. Maarouf, K.
869　　　　E. Smoyer-Tomic, D. Waltner-Toews, and D. Charron. 2005. A dynamic population
870　　　　model to investigate effects of climate on geographic range and seasonality of the tick
871　　　　*Ixodes scapularis*. International Journal for Parasitology 35:375–389.

872　Ogden, N. H., and L. R. Lindsay. 2016. Effects of climate and climate change on vectors and
873　　　　vector-borne diseases: Ticks are different. Trends in Parasitology 32:646–656.

874   Ogden, N. H., L. R. Lindsay, G. Beauchamp, D. Charron, A. Maarouf, C. J. O'Callaghan, D.
875   Waltner-Toews, and I. K. Barker. 2004. Investigation of relationships between
876   temperature and developmental rates of tick *Ixodes scapularis* (Acari: Ixodidae) in the
877   laboratory and field. Journal of Medical Entomology 41:622–633.

878   Ogden, N. H., A. Maarouf, I. K. Barker, M. Bigras-Poulin, L. R. Lindsay, M. G. Morshed, C. J.
879   O'Callaghan, F. Ramay, D. Waltner-Toews, and D. F. Charron. 2006. Climate change
880   and the potential for range expansion of the Lyme disease vector *Ixodes scapularis* in
881   Canada. International Journal for Parasitology 36:63–70.

882   Ogden, N. H., M. Radojevic´, X. Wu, V. R. Duvvuri, P. A. Leighton, and J. Wu. 2014a.
883   Estimated effects of projected climate change on the basic reproductive number of the
884   Lyme disease vector *Ixodes scapularis.* Environmental Health Perspectives 122:631–638.

885   Ogden, N. H., L. St-Onge, I. K. Barker, S. Brazeau, M. Bigras-Poulin, D. F. Charron, C. M.
886   Francis, A. Heagy, R. Lindsay, A. Maarouf, P. Michel, F. Milord, C. J. O'Callaghan, L.
887   Trudel, and A. Thompson. 2008. Risk maps for range expansion of the Lyme disease
888   vector, *Ixodes scapularis*, in Canada now and with climate change. International Journal
889   of Health Geographics 7:24.

890   Ogden, N., J. Koffi, Y. Pelcat, and L. Lindsay. 2014b. Environmental risk from Lyme disease in
891   central and eastern Canada: a summary of recent surveillance information. Canada
892   Communicable Disease Report 40:74–82.

893   Ostfeld, R., and J. Brunner. 2015. Climate change and *Ixodes* tick-borne diseases of humans.
894   Philosophical Transactions of the Royal Society B: Biological Sciences 370:20140051.

895   Ostfeld, R. S. 1997. The ecology of Lyme-disease risk: Complex interactions between seemingly
896   unconnected phenomena determine risk of exposure to this expanding disease. American
897   Scientist 85:338–346.

898   Padgett, K. A., and R. S. Lane. 2001. Life cycle of *Ixodes pacificus* (Acari: Ixodidae): Timing of
899   developmental processes under field and laboratory conditions. Journal of Medical
900   Entomology 38:684–693.

901   Peavey, C. A., and R. S. Lane. 1996. Field and laboratory studies on the timing of oviposition
902   and hatching of the western black-legged tick, *Ixodes pacificus* (Acari: Ixodidae).
903   Experimental and Applied Acarology 20:695–711.

904   Porretta, D., V. Mastrantonio, S. Amendolia, S. Gaiarsa, S. Epis, C. Genchi, C. Bandi, D.
905   Otranto, and S. Urbanelli. 2013. Effects of global changes on the climatic niche of the
906   tick *Ixodes ricinus* inferred by species distribution modelling. Parasites & Vectors 6:271.
907   Prusinski, M. A., H. Chen, J. M. Drobnack, S. J. Kogut, R. G. Means, J. J. Howard, J. Oliver, G.
908   Lukacik, P. B. Backenson, and D. J. White. 2006. Habitat structure associated with
909   *Borrelia burgdorferi* prevalence in small mammals in New York state. Environmental
910   Entomology 35:308–319.
911   Purse, B. V., P. S. Mellor, D. J. Rogers, A. R. Samuel, P. P. C. Mertens, and M. Baylis. 2005.
912   Climate change and the recent emergence of bluetongue in Europe. Nature Reviews
913   Microbiology 3:171–181.
914   Raghavan, R. K., K. Almes, D. G. Goodin, J. A. Harrington, and P. W. Stackhouse. 2014.
915   Spatially heterogeneous land cover/land use and climatic risk factors of tick-borne feline
916   cytauxzoonosis. Vector-Borne and Zoonotic Diseases 14:486–495.
917   Rand, P. W., M. S. Holman, C. Lubelczyk, E. H. Lacombe, A. T. DeGaetano, and R. P. Smith.
918   2004. Thermal accumulation and the early development of *Ixodes scapularis*. Journal of
919   Vector Ecology:13.
920   Randolph, S. E. 1997. Abiotic and biotic determinants of the seasonal dynamics of the tick
921   *Rhipicephalus appendiculatus* in South Africa. Medical and Veterinary Entomology
922   11:25–37.
923   Randolph, S. E. 2004. Tick ecology: processes and patterns behind the epidemiological risk
924   posed by ixodid ticks as vectors. Parasitology 129:S37–S65.
925   Randolph, S. E. 2010. To what extent has climate change contributed to the recent epidemiology
926   of tick-borne diseases? Veterinary Parasitology 167:92–94.
927   Randolph, S. E., R. M. Green, A. N. Hoodless, and M. F. Peacey. 2002. An empirical
928   quantitative framework for the seasonal population dynamics of the tick *Ixodes ricinus*.
929   International Journal for Parasitology 32:979–989.
930   Randolph, S. E., and K. Storey. 1999. Impact of microclimate on immature tick-rodent host
931   interactions (Acari: Ixodidae): Implications for parasite transmission. Journal of Medical
932   Entomology 36:741–748.

Ricketts, T. H., E. Dinerstein, D. M. Olson, W. Eichbaum, C. J. Loucks, K. Kavanaugh, P. Hedao, P. Hurley, D. DellaSalla, R. Abell, K. Carney, and S. Walters. 1999. Terrestrial ecoregions of North America: A Conservation Assessment. Island Press.

Rizzoli, A., H. Hauffe, G. Carpi, G. Vourc'h, M. Neteler, and R. Rosa. 2011. Lyme borreliosis in Europe. Euro Surveillance 16.

Robinson, S. J., D. F. Neitzel, R. A. Moen, M. E. Craft, K. E. Hamilton, L. B. Johnson, D. J. Mulla, U. G. Munderloh, P. T. Redig, K. E. Smith, C. L. Turner, J. K. Umber, and K. M. Pelican. 2015. Disease risk in a dynamic environment: The spread of tick-borne pathogens in Minnesota, USA. EcoHealth 12:152–163.

Rodgers, S. E., C. P. Zolnik, and T. N. Mather. 2007. Duration of exposure to suboptimal atmospheric moisture affects nymphal blacklegged tick survival. Journal of Medical Entomology 44:372–375.

Rogelj, J., M. Meinshausen, and R. Knutti. 2012. Global warming under old and new scenarios using IPCC climate sensitivity range estimates. Nature Climate Change 2:248–253.

Rogers, D. J., and S. E. Randolph. 2006. Climate change and vector-borne diseases. Pages 345–381 Advances in Parasitology. Elsevier.

Roiz, D., M. Neteler, C. Castellani, D. Arnoldi, and A. Rizzoli. 2011. Climatic Factors Driving Invasion of the tiger mosquito (*Aedes albopictus*) into new areas of Trentino, Northern Italy. PLoS ONE 6:e14800.

Rosenberg, R., N. P. Lindsey, M. Fischer, C. J. Gregory, A. F. Hinckley, P. S. Mead, G. Paz-Bailey, S. H. Waterman, N. A. Drexler, G. J. Kersh, H. Hooks, S. K. Partridge, S. N. Visser, C. B. Beard, and L. R. Petersen. 2018. Vital Signs: Trends in Reported Vectorborne Disease Cases — United States and Territories, 2004–2016. Morbidity and Mortality Weekly Report 67:496–501.

Salkeld, D. J., and R. S. Lane. 2010. Community ecology and disease risk: lizards, squirrels, and the Lyme disease spirochete in California, USA. Ecology 91:293–298.

Samir, K. C, and Lutz, W. 2017. The human core of the shared socioeconomic pathways: Population scenarios by age, sex and level of education for all countries to 2100. Global Environmental Change 42:181–192.

Schauber, E. M., R. S. Ostfeld, and A. S. E. Jr. 2005. What is the best predictor of annual Lyme disease incidence: Weather, mice, or acorns? Ecological Applications 15:575–586.

964   Schmidt, G. A., M. Kelley, L. Nazarenko, R. Ruedy, G. L. Russell, I. Aleinov, M. Bauer, S. E.
965   Bauer, M. K. Bhat, R. Bleck, V. Canuto, Y.-H. Chen, Y. Cheng, T. L. Clune, A. Del
966   Genio, R. de Fainchtein, G. Faluvegi, J. E. Hansen, R. J. Healy, N. Y. Kiang, D. Koch, A.
967   A. Lacis, A. N. LeGrande, J. Lerner, K. K. Lo, E. E. Matthews, S. Menon, R. L. Miller,
968   V. Oinas, A. O. Oloso, J. P. Perlwitz, M. J. Puma, W. M. Putman, D. Rind, A. Romanou,
969   M. Sato, D. T. Shindell, S. Sun, R. A. Syed, N. Tausnev, K. Tsigaridis, N. Unger, A.
970   Voulgarakis, M.-S. Yao, and J. Zhang. 2014. Configuration and assessment of the GISS
971   ModelE2 contributions to the CMIP5 archive. Journal of Advances in Modeling Earth
972   Systems 6:141–184.
973   Schulze, T. L., R. A. Jordan, and R. W. Hung. 2001. Effects of selected meteorological factors
974   on diurnal questing of *Ixodes scapularis* and *Amblyomma americanum* (Acari: Ixodidae).
975   Journal of Medical Entomology 38:318–324.
976   Scott, J., and C. Scott. 2018. Lyme disease propelled by *Borrelia burgdorferi*-infected
977   blacklegged ticks, wild birds and public awareness ─ not climate change. Journal of
978   Veterinary Science & Medicine 6:01–08.
979   Smith, J. R., A. D. Letten, P.-J. Ke, C. B. Anderson, J. N. Hendershot, M. K. Dhami, G. A. Dlott,
980   T. N. Grainger, M. E. Howard, B. M. L. Morrison, D. Routh, P. A. S. Juan, H. A.
981   Mooney, E. A. Mordecai, T. W. Crowther, and G. C. Daily. 2018. A global test of
982   ecoregions. Nature Ecology & Evolution 2:1889–1896.
983   Sohl, T. 2019. The next generation of land-cover projections for the conterminous United States.
984   Sohl, T. L., K. L. Sayler, M. A. Bouchard, R. R. Reker, A. M. Friesz, S. L. Bennett, B. M.
985   Sleeter, R. R. Sleeter, T. Wilson, C. Soulard, M. Knuppe, and T. V. Hofwegen. 2014.
986   Spatially explicit modeling of 1992–2100 land cover and forest stand age for the
987   conterminous United States. Ecological Applications 24:1015–1036.
988   Sonenshine, D. E., and R. M. Roe. 2013. Biology of Ticks. OUP USA.
989   Stafford, K. C. 1994. Survival of immature *Ixodes scapularis* (Acari: Ixodidae) at different
990   relative humidities. Journal of Medical Entomology 31:310–314.
991   Subak, S. 2003. Effects of climate on variability in Lyme disease incidence in the Northeastern
992   United States. American Journal of Epidemiology 157:531–538.
993   Swei, A., L. I. Couper, L. L. Coffey, D. Kapan, and S. Bennett. 2019. Patterns, drivers, and
994   challenges of vector-borne disease emergence. Vector-Borne and Zoonotic Diseases.

995   Tabachnick, W. J. 2010. Challenges in predicting climate and environmental effects on vector-
996   borne disease episystems in a changing world. Journal of Experimental Biology 213:946–
997   954.

998   Taylor, K. E., R. J. Stouffer, and G. A. Meehl. 2012. An overview of CMIP5 and the experiment
999   design. Bulletin of the American Meteorological Society 93:485–498.

1000   Tuite, A. R., A. L. Greer, and D. N. Fisman. 2013. Effect of latitude on the rate of change in
1001   incidence of Lyme disease in the United States. CMAJ Open 1:E43–E47.

1002   Vail, S. G., and G. Smith. 1998. Air temperature and relative humidity effects on behavioral
1003   activity of blacklegged tick (Acari: Ixodidae) nymphs in New Jersey. Journal of Medical
1004   Entomology 35:1025–1028.

1005   Vandyk, J. K., D. M. Bartholomew, W. A. Rowley, and K. B. Platt. 1996. Survival of *Ixodes*
1006   *scapularis* (Acari: Ixodidae) exposed to cold. Journal of Medical Entomology 33:6–10.

1007   van Vuuren, D. P., J. Edmonds, M. Kainuma, K. Riahi, A. Thomson, K. Hibbard, G. C. Hurtt, T.
1008   Kram, V. Krey, J.-F. Lamarque, T. Masui, M. Meinshausen, N. Nakicenovic, S. J. Smith,
1009   and S. K. Rose. 2011. The representative concentration pathways: an overview. Climatic
1010   Change 109:5–31.

1011   Wenger, S. J., D. J. Isaak, J. B. Dunham, K. D. Fausch, C. H. Luce, H. M. Neville, B. E. Rieman,
1012   M. K. Young, D. E. Nagel, D. L. Horan, and G. L. Chandler. 2011. Role of climate and
1013   invasive species in structuring trout distributions in the interior Columbia River Basin,
1014   USA. Canadian Journal of Fisheries and Aquatic Sciences 68:988–1008.

1015   Wenger, S. J., and J. D. Olden. 2012. Assessing transferability of ecological models: an
1016   underappreciated aspect of statistical validation. Methods in Ecology and Evolution
1017   3:260–267.

1018   Wilking, H., and K. Stark. 2014. Trends in surveillance data of human Lyme borreliosis from six
1019   federal states in eastern Germany, 2009–2012. Ticks and Tick-borne Diseases 5:219–224.

1020   Wimberly, M. C., M. J. Yabsley, A. D. Baer, V. G. Dugan, and W. R. Davidson. 2008. Spatial
1021   heterogeneity of climate and land-cover constraints on distributions of tick-borne
1022   pathogens. Global Ecology and Biogeography 17:189–202.

1023   World Health Organization. 2014. A global brief on vector-borne diseases. World Health
1024   Organization Technical Report.

1025   Yamashita, T., K. Yamashita, and R. Kamimura. 2007. A stepwise AIC method for variable
1026   selection in linear regression. Communications in Statistics - Theory and Methods
1027   36:2395–2403.

1028   Yang, L., S. Jin, P. Danielson, C. Homer, L. Gass, S. M. Bender, A. Case, C. Costello, J. Dewitz,
1029   J. Fry, M. Funk, B. Granneman, G. C. Liknes, M. Rigge, and G. Xian. 2018. A new
1030   generation of the United States National Land Cover Database: Requirements, research
1031   priorities, design, and implementation strategies. ISPRS Journal of Photogrammetry and
1032   Remote Sensing 146:108–123.

1033   Zhang, Z. 2016. Variable selection with stepwise and best subset approaches. Annals of
1034   Translational Medicine 4:136–136.

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1037 **Tables**

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1039 **Table 1.** Climate variables considered for models of disease incidence by region, along with
1040 descriptions and justification of their relevance to disease transmission.

1041

Climate Variable	Description	Biological Relevance
Lagged winter temperature	Average monthly temperatures for Dec - Feb 1.5 years prior. Identified by Subak 2003 as significantly positively correlated with Lyme disease incidence in highly endemic areas.	Colder winter temperatures are associated with reduced host-seeking abilities of the adult tick (Duffy and Campbell 1994, Clark 1995, Carroll and Kramer 2003) and reduced abundance of the white-footed mouse, a highly competent reservoir host (Wolff 1996).
Spring precipitation	Average precipitation in May and June. Identified by McCabe and Bunnell 2004 as significantly positively correlated with Lyme disease incidence in highly endemic areas.	Greater precipitation during the late spring and early summer increases the moisture of the leaf litter, providing conditions which promote the survival and questing activity of the nymphal life stage (Knülle and Rudolph 1982, Berger et al. 2014).
Hot, dry days	The number of days with temperature > 25°C and precipitation = 0 during May – July (or May – June for counties with *Ixodes pacificus*). Identified by Burtis et al. 2016 as significantly negatively correlated with Lyme disease incidence in highly endemic areas.	Hot, dry conditions are associated with decreased questing activity and questing height of ticks (Randolph and Storey 1999, Schulze et al. 2001), reducing the likelihood of attachment to humans (Arsnoe et al. 2015). The May - July, and May - June, time periods capture the peak nymphal questing periods for *I. scapularis* and *I. pacificus*, respectively (Eisen et al. 2016).
Cumulative average temperature	The sum of average daily temperatures (°F) over the entire year	Cumulative temperature appears to control most developmental stages of *I. scapularis* (Lindsay et al. 1995, Rand et al. 2004). Lower cumulative temperature is associated with longer development periods and/or higher tick mortality (McEnroe 1977, Estrada-Peña 2002, Brownstein et al. 2003, Ogden et al. 2004, Leighton et al. 2012).
Total annual precipitation	The sum of total daily precipitation (mm) over the entire year	Greater precipitation increases the moisture of the leaf litter, providing conditions which favor tick survival and questing activity (Knülle and Rudolph 1982, Jones and Kitron 2000, Berger et al. 2014a).

Daily temperature variability	The variance in average daily temperatures (°F) over the entire year	Frequent temperature variation can decrease tick survival, even beyond that of constant cold exposure, due to energetic costs associated with adapting to changing temperatures (Gigon 1985, Hermann and Gern, 2013); however, effects will vary based on the average temperature of the region.
Daily precipitation variability	The variance in total daily precipitation (mm) over the entire year	Both drought and heavy rainfall are associated with deceased tick questing activity and survival (Randolph 1997, Jones and Kitron 2000, Perret et al. 2004). Variation in precipitation, as opposed to consistent rainfall supplying favorable high relative humidity conditions, may thus be detrimental for tick survival, but will depend on the average precipitation of the region and the magnitude of variation.

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1045 **Table 2.** Effect of climate and non-climate variables on Lyme disease incidence by region. Only
1046 variables included in the best fit model, as determined by variable selection, are shown. The
1047 scaled coefficient estimates (Coef.) shown here reflect the standard deviation change in Lyme
1048 disease incidence for a one standard deviation change in the climate variable. The coefficients
1049 are scaled so that the effects of different variables are directly comparable. The standard errors
1050 (SE) shown are clustered by the agricultural statistics district (see Methods: Statistical analysis).
1051 Statistically significant ($p < 0.05$) coefficients are denoted with *.
1052

Variable	Northeast Coef.	Northeast SE	Midwest Coef.	Midwest SE	Pacific Coef.	Pacific SE	Pacific Southwest Coef.	Pacific Southwest SE	Southwest Coef.	Southwest SE	Southeast Coef.	Southeast SE
Avg. winter temp.			-0.073	0.237	-0.967	1.039	0.119	0.172				
Avg. winter temp.^{2}			0.381	0.253	1.268	0.894	0.391	0.403				
Avg. spring precip.	0.067	0.129	-0.051	0.041			0.089	0.089	-0.998	0.836		
Avg. spring precip.^{2}	-0.094	0.083										
Hot, dry days	-0.302*	0.128	-0.264*	0.099					0.151	0.137	-0.029	0.022
Hot, dry days ^{2}	0.106	0.062	0.121*	0.055								
Cumulative temp.	1.034*	0.468							1.589	1.429	1.928	1.657
Cumulative temp.^{2}									-2.127	1.620	-2.405	1.811
Total annual precip.	-0.141	0.283	-0.046	0.176					1.192	0.981		
Total annual precip.^{2}	0.183	0.229	-0.010	0.115								
Temp. variability	0.365	0.596					0.112	0.954			0.813*	0.310
Temp. variability ^{2}	0.131	0.483					0.224	0.488			-0.473*	0.241
Precip. variability			0.040	0.048					-0.220	0.176		
Precip. variability ^{2}			0.012	0.019								
Lag 'ticks' search	0.168*	0.075	0.016	0.017	0.014	0.036	0.049	0.059	0.020	0.069	-0.016	0.019
Poverty	-0.055	0.087	0.046	0.072					0.210	0.133		
Percent insured											-0.009	0.039
Forest cover	1.988	1.283	-3.966	3.896	-1.515*	0.763	-0.365	0.513			0.663	0.383
Mixed dev. cover									1.447	1.650	1.441*	0.686
R^2	0.728		0.829		0.405		0.327		0.309		0.330	
Model with only climate and dummy variables												
R^2	0.681		0.768		0.230		0.137		0.112		0.146	
Model with only non-climate and dummy variables												
R^2	0.712		0.820		0.400		0.308		0.258		0.320	
Model with only county dummy variable												
R^2	0.606		0.700		0.156		0.114		0.090		0.149	
Model with only year dummy variable												
R^2	0.045		0.018		0.028		0.014		0.007		0.010	

1053 **Table 3**. Model validation metrics for four specifications of models of Lyme disease incidence
1054 (see Methods: Model validation). The model validation metrics shown are the root-mean-square
1055 error (RMSE) and correlation coefficient (r) for estimated versus observed Lyme disease incidence
1056 in the testing data sets. The observed and estimated average (± 1 standard deviation) annual Lyme
1057 disease incidence is also shown for each region and each model specification. Model validation
1058 was performed using data from 2008 – 2017 (the years with complete data for all predictors).
1059

	Observed annual incidence	Main Model			Model Spec. 2			Model Spec. 3			Model Spec. 4		
		Est. annual inc.	RMSE	r	Est. annual inc.	RMSE	r	Est. annual inc.	RMSE	r	Est. annual inc.	RMSE	r
NE	48.9 ± 17.4	51.3 ± 13.3	38.970	0.853	51.8 ± 15.6	39.138	0.851	49.4 ± 9.4	65.419	0.458	51.2 ± 13.2	38.343	0.858
MW	14.5 ± 3.2	12.7 ± 2.1	15.709	0.903	12.6 ± 3.1	15.706	0.902	14.2 ± 4.0	29.023	0.602	12.7 ± 2.1	15.49	0.906
PC	0.8 ± 0.3	0.8 ± 0.1	1.739	0.402	0.9 ± 0.3	1.739	0.404	0.9 ± 0.1	1.777	0.282	0.8 ± 0.1	1.736	0.423
PS	0.9 ± 0.6	0.8 ± 0.4	1.682	0.264	0.8 ± 0.4	1.682	0.268	0.8 ± 0.2	1.316	0.321	0.8 ± 0.4	1.747	0.262
SW	0.4 ± 0.3	0.4 ± 0.2	5.169	0.071	0.4 ± 0.3	5.170	0.070	0.3 ± 0.2	5.131	0.040	0.4 ± 0.2	5.157	0.086
SE	0.5 ± 0.2	0.5 ± 0.2	1.685	0.323	0.5 ± 0.2	1.694	0.313	0.5 ± 0.2	1.725	0.172	0.5 ± 0.2	1.682	0.326

1060

1061 **Table 4.** Projected change in the number of Lyme disease cases, relative to hindcasted 2010 –
1062 2020 levels, for each region under the upper and moderate climate change scenario. Lyme disease
1063 projections incorporate county-level population size projections under SSP2 for 2050 and 2100
1064 from Hauer et al. 2019 (see Tables S6 & S7). Point estimates and 95% prediction intervals are
1065 shown.
1066

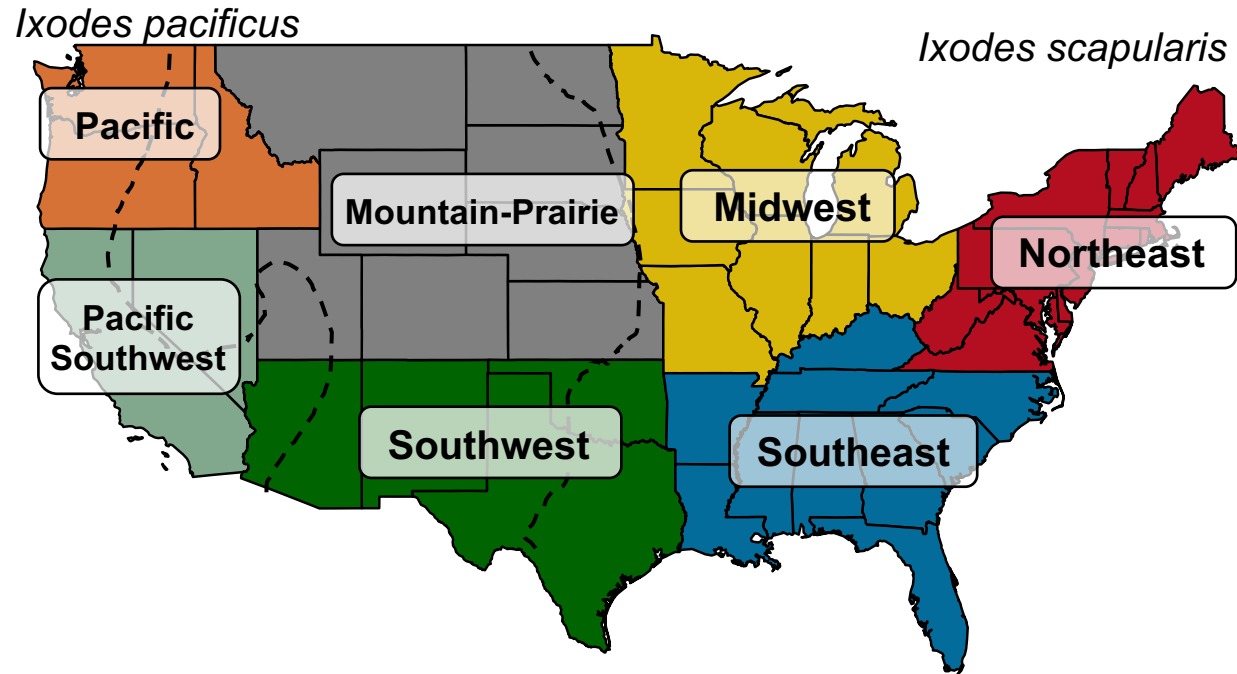|	Upper climate change scenario (RCP8.5)		Moderate climate change scenario (RCP4.5)	
	2040 – 2050	2090 – 2100	2040 – 2050	2090 - 2100
Northeast	23,619 [2,013, 45,226]	61,776 [34,197, 89,354]	7,415 [-14,646, 29,476]	-7,385 [-36,417, 21,647]
Midwest	-2,470 [-10,839, 5,899]	-4,217 [-13,681, 5,247]	2,504 [-5,633, 10,641]	477 [-10,305, 11,529]
Pacific	48 [-218, 315]	104 [-379, 587]	17 [-212, 246]	113 [-246, 471]
Pacific Southwest	-84 [1,948, 1,780]	-239 [-2,490, 2,012]	-11 [-1,726, 1,705]	90 [-2,012, 2,192]
Southwest	-148 [-1325, 1,029]	-608 [-2,434, 1,217]	-133 [-1,301, 1,034]	-240 [-1,884, 1,403]
Southeast	991 [-236, 2,217]	1,768 [-61, 3,597]	339 [-865 1,543]	776 [-807, 2,339]
US Total	22,485 [-8,585, 57,451]	33,639 [-9,916, 77,194]	10,131 [-24,383, 44,645]	-6,169 [-51,671, 39,581]

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1070 **Figure Legends**
1071

1072 **Figure 1. a)** Regional boundaries designated by US Fish & Wildlife Service. These regions were
1073 used to analyze spatial variation in the effects of climate conditions on disease outcomes. Map
1074 recreated from: https://www.fws.gov/endangered/regions/index.html. Dashed black lines denote
1075 the approximate eastern boundary of *Ixodes pacificus* and western boundary of *Ixodes scapularis*
1076 based on distribution maps created by the CDC. **b)** Regional time series of log Lyme disease
1077 incidence (the number of cases per 100,000 people in the population) from 2000 – 2017. The
1078 Mountain Prairie region is not shown here as it was removed from the analysis due to low vector
1079 presence at the start of the analysis period.
1080

1081 **Figure 2.** Projected change in Lyme disease cases by region for 2040 – 2050 and 2090 – 2100
1082 under the **a)** upper (RCP8.5) and **b)** moderate (RCP4.5) climate change scenarios. Case changes
1083 refer to raw case counts rather than incidence and indicate the average change in cases for a
1084 particular decade relative to hindcasted values for 2010 – 2020. Bars represent 95% prediction
1085 intervals. Regions are defined in Fig. 1.
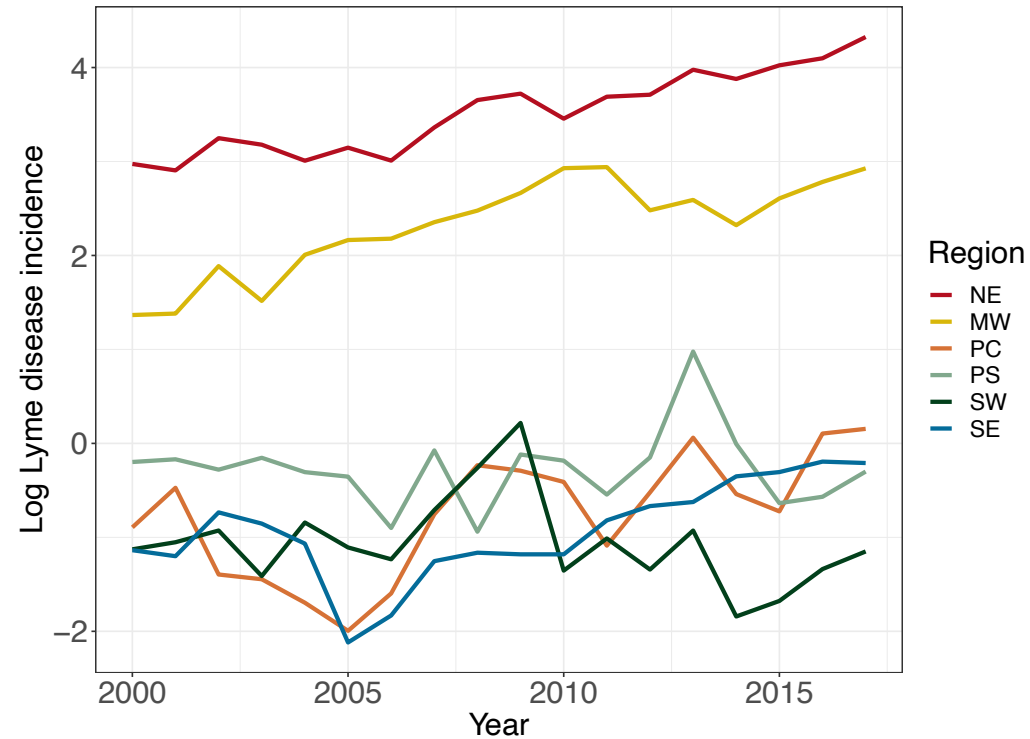1086

1087 **Figure 3.** Projected change in Lyme disease cases for 2100 shown at the county level under the
1088 **a)** upper (RCP8.5) and **b)** moderate (RCP4.5) climate change scenarios. Case changes refer to
1089 raw case counts rather than incidence and are relative to hindcasted values for 2010 – 2020. All
1090 counties within the Mountain Prairie are shown in gray as this region was not included in the
1091 analysis. Other counties shown in gray (n = 49) containing missing disease, land cover or climate
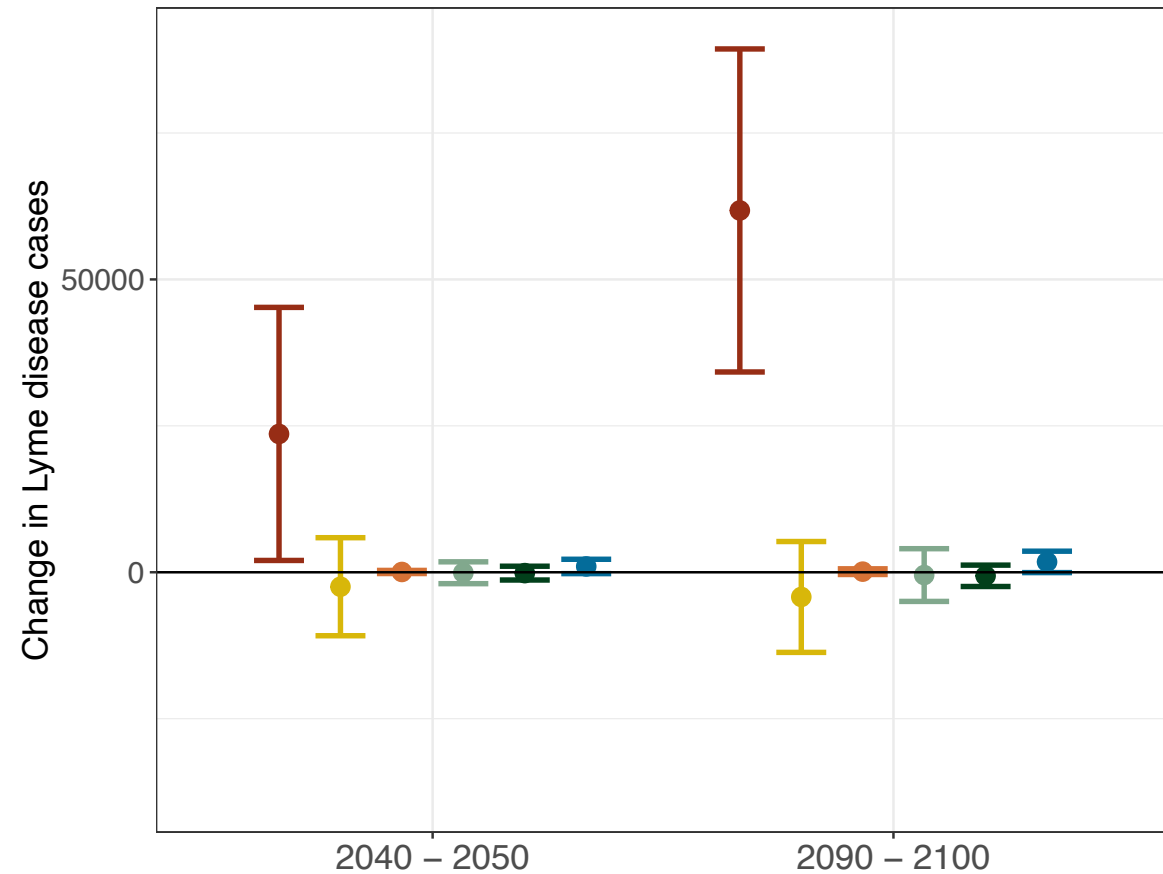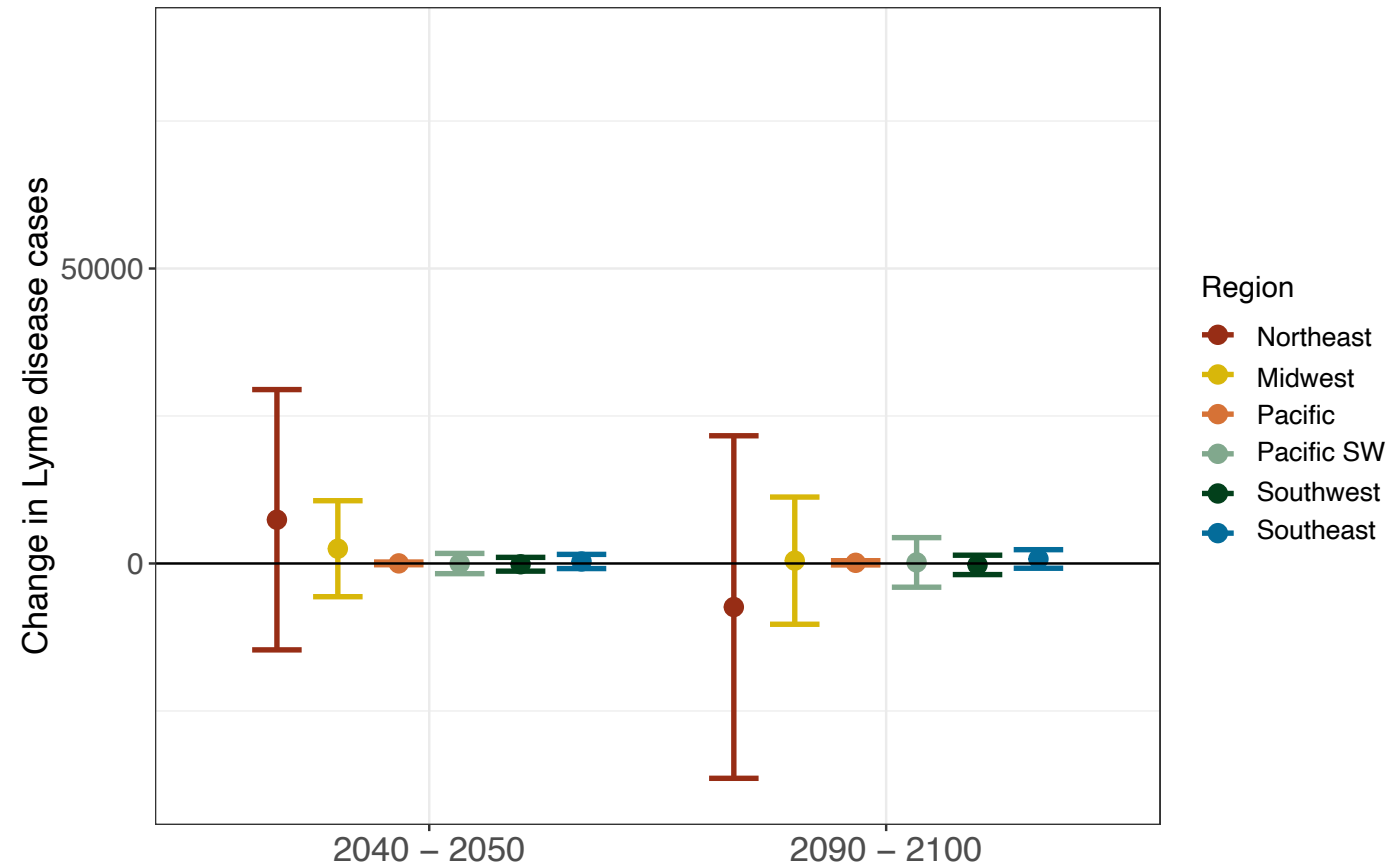1092 data.
1093
1094

a *Ixodes pacificus* ... *Ixodes scapularis*

Pacific

Mountain-Prairie   Midwest   Northeast

Pacific
Southwest

Southwest   Southeast

b Lyme disease incidence 2000 - 2017

Log Lyme disease incidence

Year

Region
NE
MW
PC
PS
SW
SE

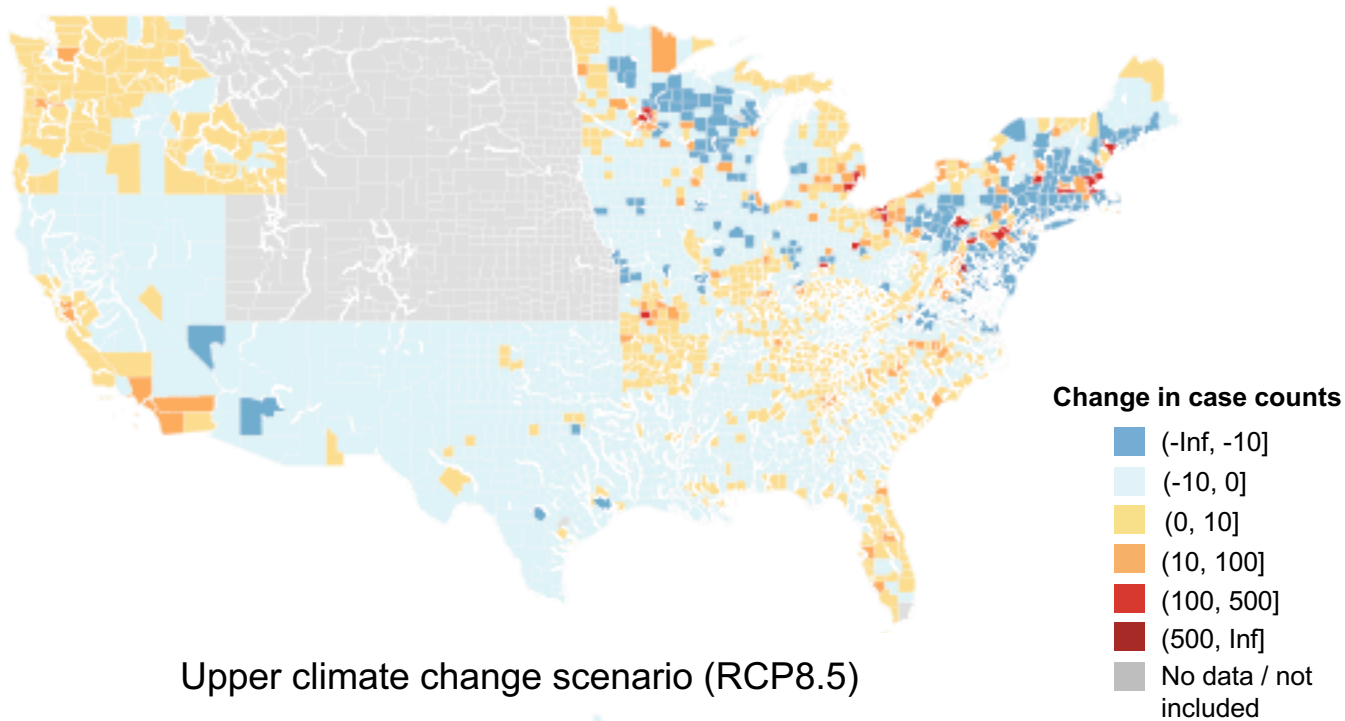**a** Upper climate change scenario (RCP8.5)

b Moderate climate change scenario (RCP4.5)

Moderate climate change scenario (RCP4.5)

Upper climate change scenario (RCP8.5)

Change in case counts

- (-Inf, -10]
- (-10, 0]
- (0, 10]
- (10, 100]
- (100, 500]
- (500, Inf]
- No data / not included